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Case report

INCIDENTAL DIAGNOSIS OF MIKULICZ DISEASE: A CASE REPORT

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ABSTRACT

Mikulicz Disease (MD) is a chronic autoimmune condition considered part of the IgG4-related disease. Its aetiology is unknown. Furthermore, like all autoimmune diseases, it predominantly affects women. MD is characterized by the abnormal enlargement of salivary and lacrimal glands. In addition, it is characterized by significant plasma cell infiltration in lacrimal and salivary glands and high IgG4 serum levels. Therefore, ultrasound (US) examination, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) may be beneficial in the diagnosis of MD. In this case report, we describe an incidental diagnosis of MD after orbit magnetic resonance in a 46 years old female patient.

KEYWORDS: *Mikulicz syndrome, Mikulicz's disease, dacryosialoadenopathy, immunoglobulin G4, Mikulicz-Radecki syndrome*

INTRODUCTION

Mikulicz Disease (MD) was first described in 1888 by Johann von Mikulicz-Radecki, a German surgeon of Polish origins (1). He reported the case of a 42-year-old man with sudden enlargement of the lacrimal gland and subsequently of the parotid and submandibular glands (2). Mikulicz believed this disease was due to an infection, while others have described MD as possibly hereditary in aetiology. Later, in 1952, Godwin hypothesized that the swollen glands were due to an accumulation of lymphoplasmacytic infiltrate in the glands, and so proposed another name: benign lymphoepithelial lesion (3, 4) (Fig. 1).

In 1933, Sjogren described histological similarities between MD and Sjogren syndrome (SS) and suggested that

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MD was a subtype of SS (5). However, subsequent studies have demonstrated immune-histological differences between the due pathologies. In particular, the absence of Sjogren's syndrome-specific SS-A and SS-B antibodies in MD and the presence of infiltration of IgG4-positive plasma cells into the gland in MD (6-9).

Since 2003, MD has been considered part of the IgG4-related autoimmune disease spectrum, which includes fibro- inflammatory injury that involves different organs such as the pancreas, bile ducts, salivary glands, lacrimal gland, periorbital tissues, kidneys, lungs, lymph nodes, pachymeninges, breast, prostate, thyroid gland, retroperitoneum, pericardium, and skin (10-13). From an epidemiological point of view, MD predominantly affects women; these patients are interested in their middle age (14). In particular, MD is defined by the symmetrical and painless bilateral salivary gland (parotids, submandibular and sublingual) and lacrimal glands enlargement (15, 16). Moreover, this condition is characterized by poor lacrimal and salivary secretion. Some patients also complain of recurrent fever (15).

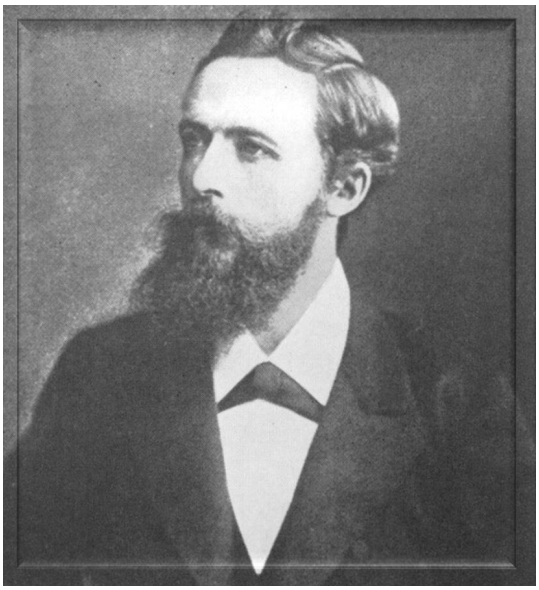

Fig. 1. *Johannes von Mikulicz-Radecki 16/05/1850 – 14/06/1905*

From a histological point of view, MD is characterized by glandular stromal hypertrophy and secretory parenchyma atrophy (17, 18). Consequently, this leads to fibrosis and hyalin infiltration. In addition, it is characterized by significant plasma cell infiltration in lacrimal and salivary glands and high IgG4 serum levels (19-21). Moreover, it is important to note that the involvement of these glands may also be found in other systemic pathologies: sarcoidosis, tuberculosis, leukaemia, and lymphosarcoma (22). Therefore, these diseases can be differentiated after the histological exam (22).

Ultrasound (US) examination of MD highlights the lacrimal and salivary glands with multiple hypoechoic areas in the enlarged glands (23). US can also be used to monitor the effectiveness of MD treatment (23). In addition, computed Tomography (CT) and Magnetic Resonance Imaging (MRI) may be beneficial in the diagnosis of MD (14, 18).

In CT, MD is characterized by bilateral lacrimal and salivary glands enlargement with no discrete lesion and homogenous enhancement. Instead, on MRI, MD is characterized by hypointense T2 and isointense T1 signals of glands (14, 18). Therefore, treatment is based on observation and systemic corticosteroid use (24, 25). In some cases, drainage and surgical removal are indicated in the specific case of strong pain (14).

The use of Glucocorticoids has been known for a long time. Its efficacy is in both reducing glandular enlargement and ameliorating glandular function. In research, it was underlined how the use of glucocorticoids markedly diminished the number of apoptotic cell s, interestingly more in MD than in SS (26); this is probably due to the characteristic reversibility process in this specific disease. Another treatment option is glandular needle aspiration (14). This procedure can be repeated multiple times and is usually the gold standard for patients with important comorbidities. Other treatments, such as conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) like methotrexate, azathioprine or mycophenolate mofetil, may be used to reduce adverse effects of long-term corticosteroids (27, 28). In addition, recent studies have shown significant efficacy of anti-CD20 monoclonal antibody rituximab in refractory patients (29). The prognosis of this condition is generally good, and it rarely evolves towards lymphoma (14). In this case report, authors describe an incidental diagnosis of MD after orbit magnetic resonance.

CASE REPORT

A 46-year-old female patient undergoes an orbit magnetic resonance (MRI) because of a sudden bilateral volumetric increase of both lacrimal glands. The MRI was performed with Siemens Magnetom AERA 1.5 T software SYNGO MR D13. Axial, sagittal and frontal planes had all been examined before and after gadolinium administration. At the MRI, a

bilateral volumetric increase of both lacrimals is visible (Fig. 2A-C). Therefore, the neuroradiologist decided to extend the exam by studying all salivary glands. They all appear symmetrically increased in volume (Fig. 3, 4A-B).

The patient also underwent an ultrasound study of salivary glands (US machine: Hitachi-Aloka Arietta v70) which confirmed the diagnostic hypothesis of MD. Symmetrical and bilateral volumetric enlargement of both the lacrimal and

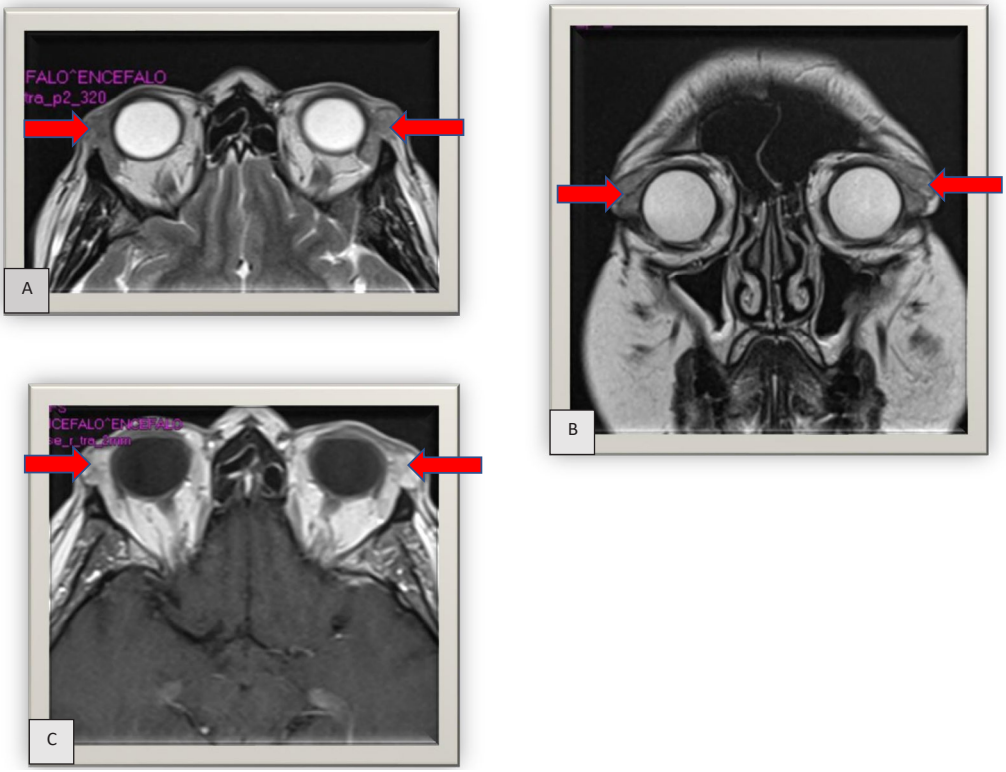

Fig. 2. ***A)****: T2 MR axial scan: volumetric increase of both lacrimal glands without alteration of their characteristic signal intensity (****arrows****);* ***B)****: T1 MR coronal scan: confirm the volumetric increase of both lacrimal glands (****arrows****);* ***C)****: T1 MR axial scan after injection of contrast medium: volumetric increase of the lacrimal glands showing intense and diffuse homogeneous enhancement after contrast injection medium (****arrows****).*

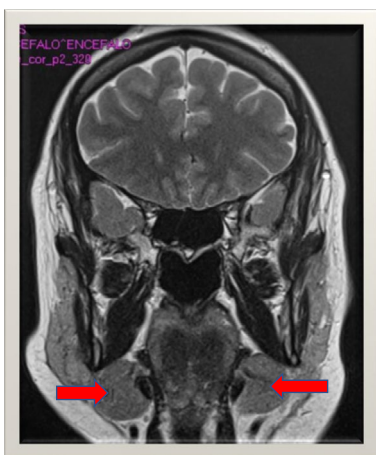

Fig 3. *RM axial scan demonstrates bilateral swelling of the submandibular glands (arrows).*

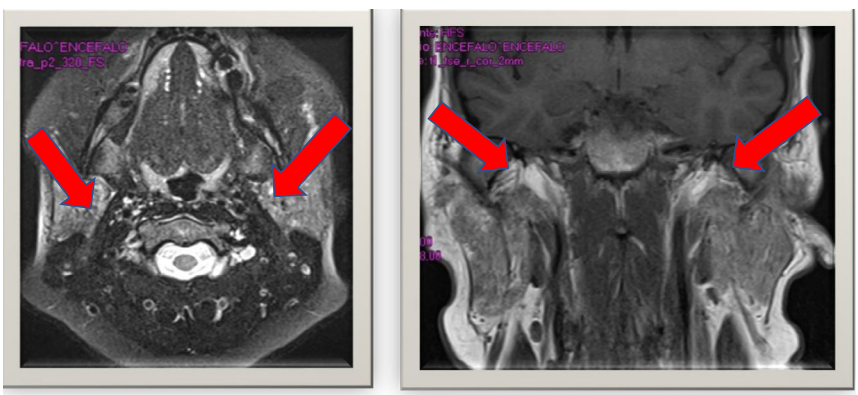

Fig 4. ***A)****: T1 MR axial scan: diffuse enlargement of the right and left parotid glands (****arrow****) with homogeneous and normal signal intensity without a focal parotid lesion;* ***B)****: T1 MR coronal scan: diffuse enlargement of the left parotid gland (****arrow****) with homogeneous and normal signal intensity without a focal parotid lesion, the right parotid also appears fairly enlarged with normal signal intensity.*

salivary glands characterizes the disease presented in this case report. Regarding the imaging, during the MRI, glands are visualized through enlarged; however, there is signal homogeneity in all sequences. More specifically, they are seen as hypointense in T2 sequences while isointense in T1 sequences. Therefore, no hyperintense areas are visualized in this kind of disease.

On the other hand, after gadolinium injection, the whole glands are homogeneously visualized as enhanced. Specifically: no lesions are visible in the part of the facial nerve crossing the parotid gland. Furthermore, no nervous or muscular structures are compromised despite the volumetric increase of lacrimal glands.

DISCUSSION

Immunoglobulin G4-related disease (IgG4-related disease) is a systemic immune-mediated fibroinflammatory pathology that involves various organs (30). Since its discovery in 2003, numerous conditions recognized as separate entities for decades, such as Mikulicz disease, are individual manifestations of IgG4-related disease based on shared histopathology (31). It is an autoimmune disease mainly affecting women between 40 and 60 (32).

The unique histopathological features of the IgG4-related disease are systemic inflammation, lymphoplasmacytic infiltration with IgG4-positive plasma cells, phlebitis and storiform fibrosis associated with elevated serum IgG4 concentrations in approximately 70% of patients (18).

Typical clinical presentation of MD is represented by symmetric enlargement of the lacrimal and glands associated with a reduction in the production of tears (xerophthalmia) and saliva (xerostomia) (30). Therefore, from a diagnostic point of view, IgG4 immunostaining should be performed in all tissue specimens where IgG4-RD is on the differential diagnosis (18, 30).

The 2019 American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) classification criteria for IgG incorporate histopathological findings and clinical context for diagnosis of this pathology (33). In addition, this clinical case underlines the importance of diagnostic tests such as US, CT and MRI to obtain an early diagnosis of this rare pathology (14, 23).

CONCLUSIONS

In the case discussed, the patient did not complain of any previously described symptoms except a sudden volumetric increase of lacrimal glands. Since it was also visible at the objective exam, the general physician prescribed her an Orbit MRI. The extension of the exam to salivary glands, the US exam and the elevated IgG4 serum allowed the formulation of a quick diagnosis and, therefore, to proceed to immediate treatment. The patient was treated with glucocorticoids. She recovered in a short time, and she then proceeded with her follow-up.

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